REMARKS

Claims 33 and 35-42 are pending and under examination. Applicant has herein amended claim 33. This amendment does not involve any issue of new matter. Support for this amendment may be found *inter alia* as follows: table 3 on page 103, page 44, lines 8-15, and figures 28-37. Accordingly, entry of this amendment is respectfully requested.

Rejection under 35 USC 112, second paragraph

Claims 33 and 35-42 were rejected as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter of the invention. The Office Action states that it is unclear what the conditions are for the in vitro incubation.

In response, applicant respectfully traverses the above rejection. Nevertheless, applicant without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have herein amended the claims in accordance with the Examiner's suggestion to recite "...remain attached in vitro after incubation for 5 days at 37 °C in either (i) human, mouse or fetal serum, or (ii) phosphate buffered saline with 5 mg/ml bovine serum albumin." Applicant notes that the claims as amended provide the incubation conditions, *e.g,* the claim recites, *inter alia*, the (a) incubation temperature, (b) incubation time, and (c) incubation solutions. Applicant submits that the claims are sufficiently definite such that one skilled in the art would fully understand what applicants regard as the invention.

Rejection under 35 USC 112, first paragraph

Claims 33 and 35-42 were rejected as allegedly not being enabled by the specification. In particular, the Office Action states that the specification does not enable antibodies with a kinase site other than either at position 224 or at the C-terminus of the linear amino acid sequence in a heavy chain. *See* pages 4-5.

In response, applicant respectfully traverses the above rejection. Applicant submits the specification would have enabled one skilled in the art make the claimed antibodies as of the

application's May 31, 2000 priority date. In support, applicants attach hereto as **Exhibit 1** a Declaration under 37 C.F.R. ' 1.132 of Mark Walter, Ph.D (referred to as the "Declaration"). Dr. Walter is an Associate Professor of Microbiology and Structural Biology at the University of Alabama. As evident from his curriculum vitae, Dr. Walter is skilled in the art of protein crystallography and molecular modeling. Dr. Walter states in the Declaration that based on applicants' specification and what he knew as of May 31, 2000, *i.e.* applicants' priority date, he would have been able to make, without undue experimentation, an antibody with a kinase recognition site at a position other than serine 224 or in the carboxy terminus, such as in the hinge region. *See* paragraph 6 of Declaration. In other words, Dr. Walter states that he would have been able to make applicants claimed invention based on his knowledge and the teachings in the specification as of the priority date. Accordingly, applicant submits that the specification enables the full scope of the claimed invention.

The Office Action states that the specification teaches that structural distortions may result from the attachment of phosphate groups to antibodies and it is extremely difficult to get the crystal structure of an intact antibody, and the phosphoserine bond at position 224 in the new construct is highly resistant to hydrolysis. *See* page 4 of Office Action. Applicant points out that Dr. Walter notes in the Declaration that the examples and methods provided in the specification would allow a skilled artisan to adopt the methodology to scan the entire antibody backbone, including the hinge region, for those locations where the phospohserine or other phospho-amino stability is favored, and thus be able to insert a kinase site at any region of the antibody and then examine the local phospho interactions. *See* paragraph 8 of Declaration.

With respect to the specific comment in the Office Action that it is extremely difficult to get the crystal structure of an intact antibody (*see* paragraph 8 of the Office Action), applicant notes that Dr. Walter notes the distinction between crystallizing a protein and performing homology modeling of a protein based on crystal structure. Dr. Walter comments that applying homology modeling based on a published monoclonal antibody is not unduly difficult since the published monoclonal antibody serves as a template. Thus utilizing the homology modeling approach to predict sites for kinase insertion is routine. *See* paragraph 10 of Declaration. Dr Walter then states that any residue in the entire protein, including the hinge region, can be homology modeled using the methodology described in the specification, and that the inclusion

of the molecular modeling approach *reduces* the experimentation by *removing* the preliminary guesswork or random searching that would be required to develop monoclonal antibodies with a stable phosphorylation site. *See* paragraphs 11-12 of Declaration. The molecular modeling approach focuses the effort on those amino acid regions that fit the modeling criteria as described in the specification; the serine 224 example is evidence that once the homology modeling approach yields a site that appears to foster increased stability, the remaining work of producing and testing the molecule is straightforward and widely practiced. *See* paragraph 12 of Declaration.

Accordingly, in view of the above comments and the attached Declaration, applicant submits that the specification would have enabled one skilled in the art, as of May 31, 2000, to make a phosphorylatable antibody or antigen binding fragment thereof, engineered to include at least one heterologous kinase recognition site located in the hinge region and which does not reduce the ability of the antibody or antigen binding fragment to bind antigen, such that an added phosphate group of a phosphorylated form of the antibody or antigen binding fragment is protected from hydrolysis by intramolecular interactions with other amino acid residues so that at least 80% of all the phosphate groups remain attached after at least 5 days of incubation. Accordingly, the claimed invention is enabled. Applicant respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 USC 112, second paragraph

Claims 33 and 35-42 were rejected as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter of the invention. The Office Action states that the claims are indefinite, alleging that it is not clear whether the antibody retains full or partial binding.

In response, applicant respectfully traverses the Examiner's above rejection. Applicant submits that the claims as drafted were sufficiently clear. Nevertheless, applicant without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application has herein amended the claims to recite "...which does not **reduce** the ability..." [emphasis added]. Applicant submits that the amended claim is clear in that the heterologous kinase recognition site does not reduce the ability of the antibody, or antigen binding fragment